Pacini Editore & AU CNS

Case Report

Heroin Addict Relat Clin Probl 20xx; xx(x): xx-xx

HEROIN ADDICTION & RELATED CLINICAL PROBLEMS
www.europad.org
www.wftod.org

Diagnosis of neonatal abstinence syndrome: Substance use during pregnancy

Joanne Thomas and Kim Wolff

King's College London, Institute of Pharmaceutical Science, Faculty of Life Sciences & Medicine, London, UK

Summary

Introduction: Internationally the misuse of prescribed medications is becoming a significant public health problem. The misuse of opioid analgesics is especially problematic with their use in pregnancy a growing but under reported problem. **The Case:** A male neonate (3.485 kg) suffered poor feeding, gastro-intestinal disturbance, hypoglycaemia, and respiratory distress. During pregnancy his mother was prescribed a variety of psychoactive medications including an opiate analgesic (co-codamol), an antidepressant (citalopram), an antipsychotic (chlorpromazine) and a benzodiazepine receptor agonist (zolpidem). A diagnosis of Neonatal Abstinence Syndrome (NAS) was made following a postnatal disclosure of unquantified maternal tramadol misuse in pregnancy. **Conclusions:** It is important to recognise the risk of prescribed medication misuse during pregnancy and the impact these drugs may have on the fetus and neonate. A NAS following intrauterine exposure to opioid analgesics has been described clearly in the literature but evidence is limited to case studies and case series. The management of these neonates should include a full maternal medication history, supported by neonatal toxicology, with an applied understanding of the potential neonatal consequences of different intrauterine medication exposures.

Key Words: Neonatal abstinence syndrome; pregnancy; substance misuse; polypharmacy; tramadol; zolpidem

1. Introduction

The misuse of prescribed drugs is a growing problem globally, especially in high income countries, with the rates of misuse tripling since 1990 [29]. Prevalence of prescribed medication misuse is particularly high in the United States where the rate of misuse is predicted to be over four times that seen in Europe; in the US the prevalence of prescribed medication misuse is now second only to cannabis [25]. A 2012 systematic review observed that the main type of medications abused in Europe were analgesics, opioid substitution drugs and sedative/hypnotics [4].

Internationally prescribed medication and illicit drug use in pregnancy is a common but significantly under reported occurrence. It is estimated that potentially 40% of women take prescribed medications during pregnancy with chronic conditions such as depression, hypertension and asthma being the most commonly treated [5]. In one European study 1.9% of pregnant women declared illicit drug use whilst 3rd trimester hair strand analysis identified 16% of women to be positive for illicit drugs [11]. Alcohol, cannabis and prescription opioid analgesics were identified as the most commonly used drugs in pregnancy by one US prospective study with prevalence rates of 6%, 4% and 3.7% respectively; the detection rates of prescription opioids were increased whilst cannabis was reduced and alcohol unchanged [19]. Between 1999 and 2006 in the US fatal poisonings involving prescription opioid analgesics more than tripled [30]. Reflecting both the increase in use of prescribed

Corresponding author: Kim Wolff, Institute of Pharmacological Science; Faculty of Life Sciences & Medicine, King's College London, SE1 9NH, London, UK, EU.
E-mail: kim.wolff@kcl.ac.uk

medications in pregnancy and the increased rates of fatal poisonings is the level of detection of prescribed opioids (30% of cases) in post-mortem samples of pregnant women with 'non-natural' causes of death [13].

The incidence of depression has been observed to be higher within populations of US women receiving prescriptions for opioid analgesics during pregnancy than within the population of women who do not [23]. This raises concerns regarding the co prescribing of opioid analgesics and antidepressants during pregnancy and the potential for adverse neonatal outcomes. The overall absolute risk of NAS secondary to prescription opioid exposure during pregnancy is predicted to be low (5.9 per 1000 deliveries) but increased by the incidental exposure to additional risk factors which include psychotropic medication [8]. Specifically exposure to selective serotonin reuptake inhibitors (SSRIs), cigarettes and cumulative opioid exposure are all associated with an increased risk of NAS [23].

2. The Case

A married multi-parous woman (Gravida 4, Para 3) of South Asian descent aged 35 years was referred to a specialist peri-natal service providing care to pregnant substance misusers due to concerns regarding over-use of prescribed co-codamol. The patient described episodes of severe anxiety for which she would self-medicate with co-codamol due to a belief that paracetamol had anxiolytic properties. The patient reported taking up to eight co-codamol tablets (240mg codeine / 4g paracetamol) as a single dose during these episodes which would occur several times a month. Treatment with co-codamol (30mg codeine/500mg paracetamol two tablets QDS) had been commenced by the patient's General Practitioner for the symptom of back pain two years previously. There was no history of other physical health problems; hepatitis and HIV screening were negative. There was a history of post-natal depression associated with her previous pregnancy but no record of formal psychiatric assessment or diagnosis. There was no history of illicit drug misuse, smoking or alcohol consumption. The patient declined 'agonist opioid' treatment and was subsequently transferred onto a prescribed opioid. ICD 10 CM F11.20 (opioid dependence, uncomplicated) was diagnosed and the patient stabilised and maintained on 180 mg codeine daily throughout pregnancy (60mg codeine TDS): lower doses resulted in breakthrough back pain; codeine phosphate was selected to avoid unnecessary paracetamol exposure. Zolpidem (10mg nocte) was prescribed for insomnia throughout pregnancy by the patient's General Practitioner. Citalopram (20mg OM) and chlorpromazine (25mg TDS) were commenced in the third trimester for depression and agitation respectively. Throughout pregnancy maternal urine toxicology was positive for opiates only: immunoassay testing did not differentiate for codeine.

A term (40+4) male infant weighing 3.485kg (7lb 10oz) was delivered via spontaneous vaginal delivery (Apgar scores 9 + 9 at one and nine minutes respectively). Difficulty establishing an adequate feeding regime was observed from birth with the neonate displaying poor feeding; at 6 hours old he was hypoglycaemic (1.7mM/L). Initiation of breast feeding was unsuccessful and neonatal consumption of expressed breast-milk was poor (1-2mL of expressed breast milk every 3-4 hours) and compounded by vomiting. By day 6 the neonate had lost 9% of his birth weight and weighed 3.165kg. Thereon weight remained stable until day 16 (3.165kg) when it began to increase. Gastro-oesophageal reflux was diagnosed and thickeners were added to the feeds. Omeprazole (0.7mg / kg/ OD dose) was commenced on day 13 and continued during the first few months of life. Problems with reflux persisted until 6 months of age.

On day 2 the neonate became unwell: temperature 37.6°C with signs of respiratory distress. A chest x-ray showed 'streaky shadows on the right lower lobe' and the neonate was transferred to a special care facility where antibiotic and fluid therapy was commenced for a lower respiratory tract infection. Blood cultures were negative at 48 hours and all bloods including electrolytes and calcium were normal. On Day 3 the mother disclosed unquantified illicit tramadol use during pregnancy. As a direct consequence of this disclosure the mother was directed to stop breast feeding. Neonatal toxicology was positive for codeine and morphine (Codeine >500 µg/L and Morphine >500 µg/L) consistent with maternal codeine therapy. Confirmatory neonatal and /or maternal toxicology for tramadol was not available. NAS due to maternal tramadol use was diagnosed using a hospital modified version of the Finnegan withdrawal scale [10]. An earlier diagnosis of NAS had not been considered due to prescribed codeine being within the therapeutic range. Treatment with morphine sulphate (30 µg/kg 4 hourly) was commenced on day 4 following consistent NAS scores >8 and continued at this dose for three days. On day 7 it was reduced to 20 µg/kg 4 hourly for 24 hours then reduced to 10 µg/kg

4 hourly from day 8 to day 11. Treatment with morphine sulphate was terminated on Day 11 when NAS scores did not exceed 1 in 24 hours. Due to the maternal history and NAS diagnosis a social work referral was made. The mother reported no further abuse of tramadol postnatally. The neonate was discharged home aged 16 days and remains with the family unit. Signed patient consent has been obtained for this article.

3. Discussion

NAS is characterised by a collection of behavioural, cardiac and neurological signs reflecting autonomic hyper-stimulation in the neonate typically manifesting within 48-72 hours of birth [33]. NAS is most frequently associated with intrauterine exposure to heroin or methadone due to maternal use during pregnancy. However a 'neonatal abstinence syndrome' may be a consequence of intrauterine exposure to a wide variety of substances. There is no single objective confirmatory diagnostic test for NAS. Due to the constellation of clinical signs and symptoms that have been associated with the syndrome a degree of clinical subjectivity often accompanies diagnosis. NAS scoring charts commonly used in the assessment of neonates were originally designed for the assessment of babies withdrawing from methadone. Their validity in the assessment of withdrawal from other substances remains untested.

The quality of evidence regarding neonatal outcomes following antenatal exposure to psychoactive substances is variable and often based on individual retrospective case studies and unconfirmed maternal histories of drug use. However, there is evidence that in-utero exposure to codeine, tramadol, zolpidem, citalopram or chlorpromazine may result in a NAS in the neonate [12, 14, 17, 21, 22, 26, 28, 31, 32]. Symptoms associated with these syndromes are often generalised and non-specific.

Codeine is a short acting opiate which exerts a weak analgesic effect at opiate receptors that is enhanced by its partial conversion to morphine a process heavily dependent upon genetic polymorphisms of the CYP2D6 enzyme and is a process that is observed in neonates and children [6, 24]. Several case studies have been published detailing retrospective diagnoses of NAS based on a maternal history of codeine consumption. Onset of symptoms ranged from birth to 30 hours post-delivery; vomiting, poor feeding, liquid stools, tremors, irritability, restlessness, and seizures were commonly reported symptoms. In all cases symptoms improved or resolved following treatment with opiates or barbiturates and all were symptom free by day 14 [17, 21, 28].

Tramadol is an analgesic acting through mu opioid receptors with serotonin and norepinephrine reuptake inhibition. Case studies based on retrospective maternal disclosure of tramadol use during pregnancy report irritability, tremulousness, hypertonia, tachycardia, vomiting, tachypnoea, high-pitched crying and disturbed sleep-wake cycle in exposed neonates, commencing between 24-35 hours postnatally [14, 22, 32]. In all cases symptoms settled with opiate or CNS depressant treatment and did not reoccur again post discharge.

A neuroleptic discontinuation syndrome in adults following cessation of antipsychotic prescribing is described in the literature [26]. A systematic review of antipsychotic therapy during early and late pregnancy identified possible perinatal complications associated with chlorpromazine therapy in late pregnancy: as observed in this case reported symptoms included respiratory distress and fever [2]. Nausea and vomiting, predominant in this neonate, might also occur due to the discontinuation of the anti-emetic blockade of dopaminergic receptors.

Zolpidem is a hypnotic benzodiazepine receptor agonist (HBRA) that is confirmed to pass across the placenta [1]. Evidence regarding the outcomes associated with its use in pregnancy are limited. A retrospective chart study considered the outcomes of 1979 neonates exposed to benzodiazepines and/or HBRAs during early pregnancy and/or late pregnancy concluding first trimester exposure increased risk of neonatal hypoglycaemia whilst late exposure was associated with an increased risk of respiratory problems [31]. For clarity the clinical presentation in this case is recorded against the symptomatology described in the literature (Table 1).

Consequences of antenatal exposure to antidepressants has been investigated more extensively. A systematic review identified one meta-analysis and fourteen other controlled studies showing an association between gestational exposure to antidepressants and neonatal adaptation difficulties [27]. Neonatal respiratory distress was a frequently reported problem in affected infants. Other neonatal problems described included gastrointestinal and feeding disturbances and metabolic disorders including hypoglycaemia. A study considering 1602 infants who had been exposed to SSRIs in utero identified third trimester exposure to be associated with various neonatal problems including hypoglycaemia, respiratory

Table 1. Neonatal Adaptation Syndrome: A comparison of symptoms reported in literature and those observed in current case.

The maternal drug used	The maternal dose and/or dosing behaviour	Symptoms observed in the case	Symptoms reported in the literature.
Codeine	60mg TDS	Poor feeding, vomiting, irritability	Vomiting, Poor feeding, liquid stools, tremors, irritability, restlessness, seizures [17, 21, 28]
Tramadol	Unquantified	Vomiting, irritability	Irritability, tremulousness, hypertonia, tachycardia, vomiting, tachypnoea, high-pitched crying, disturbed sleep-wake cycle [14, 22, 32]
Zolpidem	10mg Nocte	Hypoglycaemia, respiratory distress	Neonatal hypoglycaemia, respiratory distress, low birth weight [31]
Citalopram	20mg OM	Hypoglycaemia, respiratory distress.	Low Apgar scores, convulsions, respiratory distress, hypoglycaemia [7, 27]
Chlorpromazine	25mg TDS	Poor feeding, irritability	Agitation, restlessness, sleepiness. Difficulties with oral feeding. [12, 26]

distress syndrome, and temperature regulation disorders [7].

In this case a diagnosis of NAS was not considered by the paediatric carers until the maternal disclosure of unconfirmed tramadol misuse during pregnancy on postnatal Day 3. It was following this maternal disclosure that a decision was made to stop breast feeding. Paediatricians felt there was insufficient information regarding the implications of breastfeeding with potential ongoing maternal tramadol misuse and polypharmacy to advocate this intervention and a review of the literature supports this [3]. Antidepressants are excreted into breast milk at low levels and a consensus exists that most are generally safe in breastfeeding [2]. Data informing the safety profiles of antipsychotic medications in breastfeeding is limited to only a few prospective and case studies detailing the outcomes of only a few neonates [18]. Direct data from studies examining the safety profile of BDRAs in breastfeeding is very limited whilst the safety of benzodiazepines in breastfeeding, especially at lower doses, seems to be established [16]. Care is required with breastfeeding in the presence of maternal codeine use as neonatal deaths and over-sedation have been observed due to the inter-individual variations in maternal codeine metabolism [20]. In cases of maternal psychoactive polypharmacy breastfeeding may have a role in attenuating the duration and severity of NAS in the neonate and it may be appropriate to consider encouraging breastfeeding as part of a care plan in these cases [9].

4. Conclusions

In this case predominant NAS symptoms were hypoglycaemia, poor feeding, gastrointestinal disturbance, and respiratory distress and it is only possible to speculate how the medications prescribed in pregnancy may have contributed to this presentation. It is likely that codeine combined with tramadol use during pregnancy contributed to NAS postnatally. Perinatal care providers need to be sensitive to the potential of neonatal complications following intrauterine exposure to commonly prescribed analgesics even within therapeutic doses. With the international increase in misuse of prescription opioids it is likely that in the future many more affected neonates will be identified and robust neonatal care pathways need to be implemented. More robust research detailing the outcomes of neonatal and child exposures to opioid analgesics and other psychoactive medications is called for: in particular cumulative effects of co-prescribed medications should be considered. The absence of specific screening tools and diagnostic testing protocols may hamper the diagnosis of NAS in exposed neonates and may lead to misdiagnosis or delayed diagnosis.

References

1. Askew, J. P. (2007). Zolpidem Addiction in a Pregnant Woman with a History of Second-Trimester Bleeding. *Pharmacotherapy.* 27 (2): 306-308
2. Becker M, Weinberger T, Chandy A, Schmukler S. (2016) Depression during Pregnancy and Postpartum. *Current Psychiatry Rep.* Mar;18 (3): 32
3. Bloor M, Paech MJ, Kaye R. (2012) Tramadol in pregnancy and lactation. *Int J Obstet Anesth.* Apr; 21(2):163-7.
4. Casati A, Sederfov R, Pfeiffer-Gerschel T. (2012) Misuse of medicines in the European Union: a systematic review of the literature. *Eur Addict Res*. 18:228-45.
5. Cleary BJ, Butt H, Strawbridge JD, Gallagher PJ, Fahey T, Murphy DJ. (2010) Medication use in early pregnancy-prevalence and determinants of use in a prospective

cohort of women. *Pharmacoepidemiol Drug Saf. 19(4): 408 - 417*

6. Crews KR, Gaedigk A, Dunnenberger HM, Klein TE, Shen DD, Callaghan JT, Kharasch ED, Skaar TC. (2011) Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Codeine Therapy in the Context of Cytochrome P450 2D6 (CYP2D6) Genotype. *Clin Pharmacol Ther.* 91 (2): 321-326
7. Davis RL, Rubanowice D, McPhillips H, Raebel MA, Andrade SE, Smith D, Yood MU, Platt R. HMO Research Network Center for Education Research in Therapeutics. (2007) Risks of congenital malformations and perinatal events among infants exposed to antidepressant medications during pregnancy. *Pharmacoepidemiol Drug Saf.* 16 (10): 1086 – 1094
8. Desai RJ, Huybrechts KF, Hernandez-Diaz S, Mogun H, Patorno E, Kaltenbach K, Kerzner LS, Bateman BT. (2015) Exposure to prescription opioid analgesics in utero and risk of neonatal abstinence syndrome: population based cohort study. *Br Med J.* 350:h2102
9. Dryden C, Young D, Hepburn M, Mactier H. (2009) Maternal methadone use in pregnancy: factors associated with the development of neonatal abstinence syndrome and implications for healthcare resources. *Br J Obstet Gynaecol* 116(5): 665-671
10. Finnegan L, Connaughton JF, Kron RE, Emich JP. (1975) Neonatal Abstinence Syndrome: Assessment and Management. *Addict Dis* 2 (1): 141-158
11. Friguls B, Joya X, Garcia-Serra J, Gomez-Culebras M, Pichini S, Martinez S, Vall O, Garcia-Algar O. (2012) Assessment of exposure to drugs of abuse during pregnancy by hair analysis in a Mediterranean island. *Addiction.* 107 (8): 1471-1479
12. Gentile S. Antipsychotic therapy during early and late pregnancy. (2008) A systematic review. *Schizophr Bull*. 36 (3): 518-544
13. Hardt N, Wong TD, Burt MJ, Harrison R, Winter W, Roth G. (2013) Prevalence of Prescription and Illicit Drugs in Pregnancy-Associated Non-natural Deaths of Florida Mothers, 1999-2005. *J Forensic Sci*. 58 (6): 1536 - 1541
14. Hartenstein S, Proquitte H, Bauer S, Bamberg C, Roehr C. (2010) Neonatal Abstinence syndrome (NAS) after intrauterine exposure to tramadol. *J Perinat Med*. 38: 695-696.
15. Ilett KF, Paech MJ, Page-Sharp M, Sy SK, Kristensen JH, Goy R, Chua S, Christmas T, Scott KL. (2008) Use of sparse sampling study design to assess transfer of tramadol and its O-desmethyl metabolite into transitional breast milk. *Br J Clin Pharmacol.* 65(5): 661-666
16. Kelly LE, Poon S, Madadi P, Koren G. (2012) Neonatal benzodiazepines exposure during breastfeeding. *J Pediatr*. 161(3):448–51
17. Khan K & Chang J. (1997) Neonatal abstinence syndrome due to codeine. *Arch Dis Child*. 76: F59-F60
18. Klinger G, Stahl B, Fusar-Poli P, Merlob P. (2013) Antipsychotic drugs and breastfeeding. *Pediatr Endocrinol Rev.* Mar-Apr; 10 (3):308-17.
19. Kreshak A, Villano J, Clark A, Deak P, Miller C. (2016) A descriptive regional study of drug and alcohol use in pregnant women using results from urine testing by liquid chromatography-tandem mass spectrometry. *Am J Drug Alcohol Abuse.* 25: 1-9
20. Madadi P, Ross CJ, Hayden MR, Carleton BC, Gaedigk A, Leeder JS, Koren G. (2009) Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study. *Clin Pharmacol Ther*. 85 (1):31–5.
21. Mangurten HH, Benawra R. (1980) Neonatal codeine withdrawal in infants of non-addicted mothers. *Pediatrics*. 65 (1): 159-160
22. Meyer FP, Rimasch H, Blaha B, Banditt P. (1997) Tramadol withdrawal in a neonate. *Eur J Clin Pharmacol*. 53: 159-160.
23. Patrick SW, Dudley J, Martin PR, Harrell FE, Warren MD, Hartmann KE, Ely EW, Grijalva CG, Cooper WO. (2015) Prescription opioid epidemic and infant outcomes. *Pediatrics.* 135 (5): 842 - 850
24. Quiding H, Olsson GL, Boreus LO, Bondesson U. (1992) Infants and young children metabolise codeine to morphine. A study after single and repeated rectal administration. *Br J Clin Pharmacol*. 33:45-49
25. SAMHSA. (2010) Results from the 2009 National Survey on Drug Use and Health: National Findings (Office of Applied Studies, NSDUH Series H – 38A, HHS Publication No. SMA 10-4586 Findings). Rockville, MD: SAMHSA
26. Tranter R. & Healy D. (1998) Neuroleptic discontinuation syndromes. *J Clin Psychopharmacol*. 12 (4): 401-406
27. Udechuka A, Nguyen T, Hill R, Szego K. (2010) Antidepressants in pregnancy: a systematic review. *Aust N Z J Psychiatry*. 44 (11): 978- 996
28. Van Leeuwen G, Guthrie R, Stange F. (1965) Narcotic withdrawal reaction in a newborn infant due to codeine. *Pediatrics*. 36: 635-636.
29. Volkow ND. (2010) Prescription Drug Abuse. National Institutes on Drug Abuse. National Institutes of Health. Department of Health & Human Services. Congress Caucus.
30. Warner M, Chen LH, Makuc DM. (2009) Increase in Fatal Poisonings Involving Opioid Analgesics in the United States, 1999-2006. *NCHS Data Brief: No 22.*
31. Wikner BN, Stiller CO, Bergman U, Asker C, Kallen B. (2007) Use of benzodiazepine receptor agonists during pregnancy: neonatal outcome and congenital malformations. *Pharmacoepidemiol Drug Saf*. 16 (11): 1203-1210
32. Willaschek C, Wolter E, Buchhorn R. (2009) Tramadol withdrawal in a neonate after long-term analgesic treatment of the mother. *Eur J Clin Pharmacol*. 65: 429-430
33. Wolff K & Perez-Montejano R. (2014) Opioid neonatal abstinence syndrome: Controversies and implications for practice. *Curr Drug Abuse Rev*. 1 (7): 44-58

Acknowledgements

None

Role of the funding source

Authors state that this study was financed with internal funds. No sponsor played a role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

The authors revised and approved the final form of the manuscript.

Conflict of interest

Authors declared no conflict of interest.

Ethics

Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. The study does not have IRB review/approval; this study does not require ethics committee approval because 'Case reports' does not require ethics committee aproval but informed consent signed by patients.

Received November 25, 2015 - Accepted May 24, 2016